Original Paper

Digestive Surgery

Dig Surg 2019;36:376–383
DOI: 10.1159/000490069

Received: December 29, 2017
Accepted: May 15, 2018
Published online: June 13, 2018

Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer

Annefleur E.M. Berkel[a] Joost M. Klaase[a] Feike de Graaff[b] Marjolein G.J. Brusse-Keizer[c] Bart C. Bongers[d] Nico L.U. van Meeteren[d, e]

[a]Department of Surgery, Medisch Spectrum Twente, Enschede, The Netherlands; [b]Faculty of Science and Technology, University of Twente, Enschede, The Netherlands; [c]Medical School Twente, Medisch Spectrum Twente, Enschede, The Netherlands; [d]Department of Epidemiology, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands; [e]Health~Holland, Topsector Life Sciences and Health, The Hague, The Netherlands

Keywords
Rectal resection · Postoperative complications · Sarcopenia · Sarcopenic obesity · Radiation attenuation · Muscle mass

Abstract
Background/Aims: To investigate the relation between skeletal muscle measurements (muscle mass, radiation attenuation, and sarcopenic obesity), postoperative morbidity, and survival after treatment of locally advanced rectal cancer. ***Methods:*** This explorative retrospective study identified 99 consecutive patients who underwent neoadjuvant chemoradiation and surgery between January 2007 and May 2012. Skeletal muscle mass was measured as total psoas area and total abdominal muscle area (TAMA) at 3 anatomical levels using the patient's preoperative computed tomography scan. Radiation attenuation was measured using corresponding mean Hounsfield units for TAMA. Sarcopenic obesity was defined as body mass index above 25 kg·m^{-2} combined with skeletal muscle mass index below the sex-specific median. Postoperative complications were graded by using the Clavien-Dindo classification. ***Results:*** Twenty-five patients (25.3%) developed a grade 3–5 complication. Lower radiation attenuation was independently associated with overall ($p = 0.003$) and grade 3–5 complications ($p = 0.002$). Sarcopenic obesity was associated with overall complications (all $p < 0.05$). Skeletal muscle measurements and survival were not significantly related. ***Conclusion:*** Radiation attenuation was associated with overall and grade 3–5 postoperative morbidity after neoadjuvant chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications.

KARGER

E-Mail karger@karger.com
www.karger.com/dsu

Annefleur E.M. Berkel
Department of Surgery, Medisch Spectrum Twente
Koningsplein 1, PO Box 50.000
NL–7500 KA Enschede (The Netherlands)
E-Mail a.berkel@mst.nl

Introduction

Treatment of locally advanced rectal cancer consists of administration of neoadjuvant chemoradiation followed by surgery [1]; this treatment method however results in 40% postoperative complication rate [2, 3]. There is increasing evidence that sarcopenia (indicated by low skeletal muscle mass, assessed by measurement of muscle cross-sectional area most often using the computed tomography [CT] scan) is associated with poor clinical outcomes. Sarcopenia is associated with increased infectious complications, prolonged hospital stay, and decreased survival rates following colorectal resection and hepatic resection for colorectal liver metastases [4, 5]. There is also strong evidence to suggest that obesity is a significant risk factor for wound and stoma site complications after colorectal surgery [6]. Combination of sarcopenia and obesity may result in even worse outcomes, since it combines the health risks of obesity and depleted lean muscle mass [7]. Sarcopenic obesity is associated with reduced functional status and survival in patients with solid tumors of respiratory and gastrointestinal tracts [7]. In patients undergoing liver resection for colorectal liver metastasis, sarcopenic obesity was associated with an increased risk of severe postoperative complications compared with patients who did not have sarcopenia [8].

Timely identification of preoperative risk factors for adverse postoperative outcome will help patients and clinicians with treatment decisions, and with the selection of patients who might have a therapeutic window that leaves room for preoperative improvement of their functional health status known to protect from postoperative side effects [9, 10]. The aim of this explorative study was to investigate the relation between skeletal muscle mass, radiation attenuation (expressed in mean Hounsfield Units [HU] for total abdominal muscle area [TAMA]) and sarcopenic obesity, and postoperative morbidity and survival after the administration of neoadjuvant chemoradiation followed by non-laparoscopic resection for rectal cancer.

Method

Patients

A retrospective study was performed including all consecutive patients with locally advanced rectal cancer who were treated with chemoradiation and surgery at our institute between January 2007 and May 2012. This is the same population dataset that we used in a previous article [11]. In the current study, however, we added data of patients' skeletal muscle mass, radiation attenuation, sarcopenic obesity, and survival.

Patients were included in the study if they had locally advanced rectal cancer (defined as a clinical T4 tumor or T3 tumor with a threatened circumferential margin (CRM ≤1 mm) and/or cN2 disease [1]) that was histologically proven with a colonoscopy and biopsy. Patients were excluded if the preoperative abdominal CT scan was missing or if the abdominal CT scan was of poor quality.

Neoadjuvant Chemoradiation and Surgery

Patients underwent a 5-week protocol of concomitant chemotherapy (825 mg·m^{-2} capecitabine twice daily) and 3D-conformal radiotherapy (50 Gy in 25 fractions). Operations were carried out by experienced colorectal surgeons according to the total mesorectal excision principle and consisted of abdominoperineal resection, low anterior resection (LAR), or rectal resection with definitive colostomy (Hartmann procedure). The considered optimal interval between chemoradiation and surgery in 2007–2010 was 6 to 8 weeks, from 2010–2011 it was 8 to 10 weeks, and since 2012, it was 10 to 12 weeks.

Outcome Variables

The baseline characteristics included are age (divided in 4 groups based on quartiles), sex, body height, body mass, American Society of Anesthesiologists (ASA) score (I-IV), Charlson comorbidity score, smoking, clinical TNM stage, neoadjuvant chemoradiation regimen, symptoms of obstruction requiring fecal diversion before rectal surgery, interval between the end of chemoradiation and resection, complications of chemoradiation, type of surgery, diverting stoma (only for patients undergoing LAR), operation time, estimated blood loss, blood transfusion intra- or postoperative, pretreatment tumor distance from the anal verge, length of hospital stay, postoperative surgical and general complications, readmission rate, mortality, pathologic tumor response, pathologic TNM stage, completeness of surgical excision (R stage), carcinoembryonic antigen (CEA) level before neoadjuvant chemoradiation, preoperative hemoglobin (Hb), skeletal muscle mass, radiation attenuation, and sarcopenic obesity.

Prespecified definitions were used to score postoperative surgical complications (until 6 months after surgery) [11]. Complications were graded by using the Clavien-Dindo classification (grade 1–5) [12, 13]. An overall complication is a grade 1–5 complication and a grade 3–5 complication is a severe complication. General complications were divided in cardiovascular, pulmonary, renal, or neurological complications.

Survival was defined as overall survival, measured in months from the day of surgery, with a follow-up of 3 years. The electronic patient record system was searched for date of death and/or the general practitioner was contacted.

Muscle Mass Measurements and Definitions

Preoperative CT scans were imported in TeraRecon (TeraRecon Aquarius; TeraRecon, USA). Skeletal muscle mass was exploratively measured at 3 levels because in the literature these different levels are used [8, 14, 15]: cross-sections at the third lumbar vertebra (L3) where both transverse processes were visible, and at both the superior and inferior border of the fourth lumbar vertebra (L4). At each level, the cross-sectional areas (cm^2) of total psoas area (TPA) and TAMA, and skeletal muscle radiation attenuation (mean HU of TAMA) were measured. TPA was measured by manually tracing and adding left and right psoas area. TAMA was manually detected and a threshold of –29 to +150 HU was applied to this region to discriminate between skeletal muscle and other tissues [16]. Muscle area and average HU were then calculated automatically. Muscle areas were normalized for the patient's body height to calculate the muscle index for TPA and TAMA in $cm^2 \cdot m^{-2}$. A lower HU value was considered to be related to a poorer overall skeletal muscle radiation attenuation, since lower HU values correspond with fatty infiltration of muscle (myosteatosis) [17]. The investigator who performed the measurements (FdG) was blinded for postoperative outcome. In the literature, the measurement of cross-sectional muscle area has shown to have a low level of inter-observer variability [18, 19]; however, their muscle measurement methodology differed from the one we followed in our study.

Sarcopenia was defined as skeletal muscle mass index (TPA or TAMA at each level) below the median, calculated for males and females separately (sex specific cut-off value) [20]. Sarcopenic obesity was defined as body mass index (BMI) above 25 $kg \cdot m^{-2}$ combined with skeletal muscle mass index, TPA, or TAMA, below the sex-specific median [20, 21].

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences for Windows (version 22.0; IBM, SPSS Inc., Chicago, IL, USA). Data are presented as mean and standard deviation for continuous normally distributed variables as checked with histograms. For continuous nonparametric variables, median and range were presented. Univariate associations between skeletal muscle mass measurements (TPA, TAMA, and radiation attenuation), sarcopenia, and sarcopenic obesity with overall and grade 3–5 postoperative complications were evaluated for significance, using Fisher exact test or chi^2 test for categorical variables and independent *t* test (if normally distributed) or Mann-Whitney U test for continuous variables. Possible confounders (see baseline characteristics above) were first tested for association with overall and grade 3–5 postoperative complications. In case they were associated with overall or grade 3–5 postoperative complications ($p < 0.150$), they were tested for association with the skeletal muscle mass measurements (TPA, TAMA, and radiation attenuation), sarcopenia, and sarcopenic obesity ($p < 0.150$). The associations between skeletal muscle mass measurements (TPA, TAMA, and radiation attenuation), sarcopenia, and sarcopenic obesity with overall and grade 3–5 postoperative complications were corrected for the remaining potential confounders in a stepwise forward multivariate logistic regression analysis. In case of multicollinearity between variables, the variable that produced the best model fit (based on the –2 log likelihood) was included in the model. Kaplan-Meier estimates and Cox regression analyses were used to assess the association between sarcopenia and sarcopenic obesity with overall survival. All baseline characteristics that were associated with either sarcopenia or sarcopenic obesity ($p < 0.150$) were tested for an association with overall survival. The variables that were also associated with survival were taken into account in the stepwise forward multivariate Cox regression analyses. Statistical significance was determined at $p < 0.05$.

Results

We identified 105 patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiation between January 2007 and May 2012. After exclusion of 6 patients (patients with disease progression, extensive comorbidity, or unresectable tumors), resection of the tumor was performed in 99 patients (96.1%, of which 53, 53.5%, males), with a median age of 66 (range 40–81) years. Sixty-four patients (64.6%) were overweight (BMI ≥25). Eleven patients (11.1%) had a BMI 30–35, and 6 patients (6.1%) had a BMI ≥35. Median (range) muscle index for TAMA at L3 was 52.2 (37.0–70.9) $cm^2 \cdot m^{-2}$ in men and 39.9 (30.2–75.4) $cm^2 \cdot m^{-2}$ in women. We were able to retrieve all data of all consecutive patients, except body height and/or body mass (n = 3, 3.0%), operation time (n = 2, 2.0%), the CEA level before neoadjuvant chemoradiation (n = 33, 33.3%), and in 4 patients (4.0%), the skeletal muscle mass/quality could not be measured on one or more levels because of vertebral screws (n = 1, 1.0%), poor quality of the CT scan (n = 1, 1.0%), or the area of interest was not completely visible on CT scan (n = 2, 2.0%). In 2 (2.0%) additional patients, the skeletal muscle mass could not be measured because their body height was unknown.

Of the 99 patients that underwent resection, 68 patients (68.7%) had an overall postoperative complication, of which 43 patients (43.4%) had a grade 1–2 complication and 25 patients (25.3%) a grade 3–5 (severe) complication. An anastomotic leakage was seen in 2 of 18 patients undergoing LAR, a sepsis was seen in 6 of the 99 patients (6.1%), and an abdominal wound complication in 17 of the 99 patients (17.2%). The mortality rate was 2.0% (2 patients). A complete overview of all postoperative complications can be found in Table 3 of our previous study [11] or in online supplementary file 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000490069). The median follow-up after surgery was 32.9 months (interquartile range 19.4–51.1 months). In the univariate relation between demographic and clinical variables and overall postoperative complications, a younger age ($p = 0.017$), an intra- or postoperative blood transfusion ($p = 0.021$), and a longer operation time ($p = 0.093$) were associated with postoperative complications ($p < 0.150$). In the univariate relation between demographic and clinical variables and grade 3–5 postoperative complications, male sex ($p = 0.032$), a higher Charlson comorbidity score ($p = 0.134$), a lower CEA score before chemoradiation ($p = 0.082$), ypT stage ($p = 0.092$), and an intra-or postoperative

Table 1. Univariate relation between skeletal muscle mass, radiation attenuation, and postoperative (grade 3–5) complications[a]

	Postoperative complication			Grade 3–5 postoperative complication		
	yes (n = 68)	no (n = 31)	p^b value	yes (n = 25)	no (n = 74)	p^b value
L3						
TPA	5.3±1.6 (n = 65)	5.5±1.7 (n = 31)	0.610	5.8±1.4 (n = 23)	5.3±1.6 (n = 73)	0.167
TAMA	47.1±9.0 (n = 65)	48.5±10.8 (n = 31)	0.516	49.0±9.4 (n = 23)	47.1±9.4 (n = 73)	0.406
Radiation attenuation[c]	34.8±8.7 (n = 67)	39.3±8.3 (n = 31)	**0.018**	32.3±8.4 (n = 24)	37.5±8.6 (n = 74)	**0.010**
L4 superior						
TPA	7.2±1.9 (n = 65)	7.5±2.4 (n = 30)	0.514	7.9±1.8 (n = 23)	7.1±2.1 (n = 72)	0.099
TAMA	48.5±9.1 (n = 65)	49.5±10.9 (n = 30)	0.641	50.1±9.2 (n = 23)	48.4±9.8 (n = 72)	0.466
Radiation attenuation[c]	35.1±8.8 (n = 67)	39.2±8.0 (n = 30)	**0.032**	32.4±8.6 (n = 24)	37.6±8.5 (n = 73)	**0.011**
L4 inferior						
TPA	7.8±2.2 (n = 64)	8.2±2.6 (n = 29)	0.531	8.6±2.0 (n = 22)	7.7±2.4 (n = 71)	0.105
TAMA	46.9±9.0 (n = 64)	47.8±11.1 (n = 29)	0.688	48.2±9.7 (n = 22)	46.9±9.7 (n = 71)	0.565
Radiation attenuation[c]	34.7±8.6 (n = 66)	40.6±12.8 (n = 29)	**0.009**	32.4±9.0 (n = 23)	37.8±10.5 (n = 72)	**0.029**

[a] Data are presented as mean ± SD.
[b] Bold entries are significant ($p < 0.05$).
[c] Radiation attenuation was measured as the mean HU of the total abdominal muscle area at the level of the third lumbar vertebra.
TPA, total psoas area in $cm^2 \cdot m^{-2}$; TAMA, total abdominal muscle area in $cm^2 \cdot m^{-2}$; HU, Hounsfield unit.

blood transfusion ($p = 0.004$) were associated with grade 3–5 postoperative complications ($p < 0.150$). A complete overview of these results can be found in Table 4 of our previous article [11] or in online supplementary file 2. An intra- or postoperative blood transfusion was not taken into account as a confounder in the multivariate analysis since the necessity of intra- or postoperative blood transfusion could be an intermediary factor between skeletal muscle mass and postoperative complications (e.g., patients could have had a blood transfusion because of a postoperative complication, for example, due to bleeding).

Postoperative Morbidity and Skeletal Muscle Mass/Quality

Skeletal muscle mass (TPA and TAMA) was not significantly associated with overall or grade 3–5 complications. In the univariate analysis, a lower skeletal muscle radiation attenuation at all 3 measurement levels was significantly associated with overall and grade 3–5 complications (Table 1). TPA at L4 superior and L4 inferior were associated ($p < 0.150$) with grade 3–5 complications and were therefore also assessed in the multivariate analysis for grade 3–5 complications. Due to multicollinearity between radiation attenuation measurements (L3, L4 inferior, and L4 superior level) and between TPA measurements (L4 inferior and L4 superior), the variable of radiation attenuation and TPA with the best model fit was included in the multivariate logistic regression analysis (radiation attenuation at L3 for both overall and grade 3–5 complications and TPA at L4 superior for grade 3–5 complications).

Of the potential confounders that were assessed for an association with overall postoperative complications, age and operation time were also associated with radiation attenuation and taken into account in the multivariate analysis for postoperative complications. In the final multivariate model (Table 2), lower skeletal muscle radiation attenuation was associated with an increased risk of overall postoperative complications (OR 0.91; 95% CI 0.85–0.97; $p = 0.003$), as was young age (OR 0.92; 95% CI 0.87–0.98; $p = 0.007$).

For postoperative grade 3–5 (severe) complications, TPA at L4 superior and radiation attenuation, as well as the potential confounders sex, Charlson comorbidity score, CEA before chemoradiation, and pathological T (ypT) stage were included in the multivariate analysis. A lower radiation attenuation (OR 0.89; 95% CI 0.83–0.96; $p = 0.002$) and a higher total psoas mass at L4 superior (OR 1.46; 95% CI 1.10–1.94; $p = 0.009$) were associated with an increased risk of grade 3–5 complications (Table 2).

Postoperative Morbidity and Sarcopenia

In the univariate analysis, sarcopenia was not significantly associated with overall and grade 3–5 postoperative complications. Sarcopenia measured as TPA at L4 superior was the only variable with $p < 0.150$ that seemed

Table 2. Univariate and multivariate relation between skeletal muscle mass, radiation attenuation, and postoperative (grade 3–5) complications[a]

	OR univariate (95% CI)	p univariate	OR multivariate (95% CI)	p multivariate
Postoperative complications				
Radiation attenuation[b]	0.94 (0.89–0.99)	0.021	0.91 (0.85–0.97)	0.003
Age, years	0.95 (0.90–1.00)	0.063	0.92 (0.87–0.98)	0.007
Operation time, min	1.01(1.00–1.02)	0.098	–	–
Grade 3-5 complications				
TPA L4 superior	1.20 (0.96–1.51)	0.103	1.46 (1.10–1.94)	0.009
Radiation attenuation[b]	0.93 (0.88–0.99)	0.013	0.89 (0.83–0.96)	0.002
Gender			–	–
Female	Ref.			
Male	2.87 (1.07–7.67)	0.036		
Charlson comorbidity score			–	–
0	Ref.			
>1	2.49 (0.98–6.36)	0.056		
CEA before CRT	0.98 (0.93–1.02)	0.318	–	–
ypT stage			–	–
ypT0–1	Ref.			
ypT2–4	0.43 (0.17–1.09)	0.076		

[a] Blood transfusion was not taken into account as a confounder in the multivariate analysis, since the necessity of intra- or postoperative blood transfusion could be an intermediary factor between skeletal muscle mass and postoperative complications.
[b] Radiation attenuation was measured as the mean HU of the total abdominal muscle area at the level of the third lumbar vertebra.
No value means that the confounder was removed from the equation because it did not significantly predict complications in the multivariate model.
TPA, total psoas area in $cm^2 \cdot m^{-2}$; CEA, carcinoembryonic antigen; CRT, chemoradiation; ypT, pathological T stage; HU, Hounsfield unit.

to be associated with grade 3–5 complications. However, in the multivariate model, this association was not statistically significant (OR 0.51; 95% CI 0.20–1.29; $p = 0.152$).

Postoperative Morbidity and Sarcopenic Obesity

In the univariate analysis, sarcopenic obesity was not significantly associated with overall complications. However, sarcopenic obesity when measured at TPA L4 superior, TAMA L3 and TAMA L4 superior were associated with overall complications with $p < 0.150$ and were therefore included in 3 separate multivariate analyses, together with confounders (age and operation time). In the final multivariate models, sarcopenic obesity measured at TPA L4 superior, TAMA L3, and TAMA L4 superior, and young age were significantly associated with postoperative complications (all $p < 0.05$; Table 3). Patients with sarcopenic obesity were 3 times more likely (ORs between 3.2 and 3.8) to develop a postoperative complication.

No significant relation was found between sarcopenic obesity and grade 3–5 (severe) complications.

Table 3. Multivariate relation between sarcopenic obesity and postoperative complications

	OR	95% CI	p value
L3			
TAMA	3.77	1.12–12.66	0.032
Age, years	0.94	0.89–0.99	0.030
L4 superior			
TPA	3.21	1.05–9.77	0.040
Age, years	0.94	0.90–1.00	0.033
L4 superior			
TAMA	3.42	1.02–11.42	0.046
Age, years	0.94	0.90–1.00	0.034

TAMA, total abdominal muscle area in $cm^2 \cdot m^{-2}$; TPA, total psoas area in $cm^2 \cdot m^{-2}$.

Overall Survival and Sarcopenia

In the univariate analysis, sarcopenia at TAMA L4 inferior was the only variable that was associated with overall survival with a $p < 0.150$ (HR 2.04; 95% CI 0.83–4.99; p =

0.120). Of all baseline characteristics (see the Method section) that were assessed for an association with overall survival, ASA, BMI, and tumor regression were also associated with sarcopenia at TAMA L4 inferior ($p < 0.150$) and taken into account in the multivariate analysis for overall survival. In the multivariate model, controlled for ASA, BMI, and tumor regression, none of the potential confounders remained in the multivariate model after the stepwise regression. Therefore, the association between sarcopenia at TAMA L4 inferior and survival remained the same.

Overall Survival and Sarcopenic Obesity

No significant relation was found between sarcopenic obesity and survival with $p > 0.337$.

Discussion

This retrospective study found that a lower skeletal muscle radiation attenuation was associated with overall and grade 3–5 (severe) postoperative morbidity after chemoradiation and resection for rectal cancer. Sarcopenic obesity was associated with overall complications. A few previous studies investigated the influence of skeletal muscle radiation attenuation on postoperative complications following colorectal cancer resection. Sabel et al. [22] showed that lower radiation attenuation was the best predictor of any complication after colectomy for colon cancer. Boer et al. [20] showed that lower radiation attenuation was associated with overall complications after open colon resection for cancer. Body composition might be of key interest to use in predicting outcomes.

More studies investigated the role of sarcopenia on complications after colorectal surgery. Sarcopenia was associated with more infectious complications [5], higher mortality [18], and decreased survival [23] after colorectal cancer resection. Reisinger et al. [24] evaluated whether low muscle mass was associated with increased inflammation after resection of colorectal malignancies by measuring inflammatory markers in plasma. They found that a low muscle mass was associated with an increased postoperative inflammatory response, which may be a part of the explanation for the high incidence of postoperative complications in sarcopenic patients [24]. In the present study, no significant relation between sarcopenia and postoperative complications was found. Sarcopenia is more than only a low skeletal muscle mass measured at a single time point. Sarcopenia is characterized by the loss of skeletal muscle mass, skeletal muscle strength, and/or physical performance [25]. Defining sarcopenia only in terms of muscle mass might be too narrow and may therefore be of limited clinical value [25]. An example is the finding in the present study that patients with a higher muscle mass (TPA at L4 superior) more often had a grade 3–5 complication. Muscle mass might be not depleted in cross-sectional area because of more fat infiltration of the muscle. Fat infiltration is the most widely accepted cause of reduced attenuation of muscle [26]. Measurement of radiation attenuation is potentially a better approach. Future research should investigate if muscle strength measurements of a muscle biopsy (rectus abdominis muscle) correlate with CT measurements.

Sarcopenic obesity could be of higher clinical use than sarcopenia alone. In the present study, sarcopenic obesity was associated with overall complications. Previously, sarcopenic obesity was found to be a predictor for grade 3–5 postoperative complications following open colon cancer surgery [20], and an independent predictor of survival in patients with solid tumors in the respiratory or gastrointestinal tract [7]. After hepatic resection for colorectal liver metastasis, patients with sarcopenic obesity had a more pronounced risk of severe complications compared with patients without sarcopenia (sarcopenic obesity 40% versus non-sarcopenia 8%, $p = 0.02$) [8]. Visser et al. [27] showed that sarcopenic obesity independently increased the risk of postoperative infections in patients undergoing cardiac surgery.

The current study underscores the importance of assessing skeletal muscle mass and quality measurements to select high-risk patients that might benefit from preoperative optimization (prehabilitation) to prevent a dismal course. Studies show that high-risk patients who were placed on a physical exercise training program before major elective surgery, improve their physical fitness [28–30], even after [31] or during [10] neoadjuvant chemoradiation in patients with rectal cancer. It remains to be seen, however, whether improving physical fitness increases skeletal muscle mass, and vice versa. Currently, in our hospital, we perform a randomized controlled trial (www.trialregister.nl, trial registration number NTR4032) to measure the effect of a 3-week prehabilitation program on postoperative complications in high-risk patients who are to undergo colorectal surgery [32], all in accordance with a part of the recent advises of Hulzebos and Van Meeteren [9]. In this trial, the effect of the prehabilitation program on muscle strength will also be investigated.

Since undergoing a CT scan is part of usual care in the work up of all patients with rectal cancer, no additional test is needed to evaluate skeletal muscle mass and radiation attenuation. Skeletal muscle mass and radiation attenuation measurements could potentially be used as a case-mix correction factor in the Dutch Surgical Colorectal Audit (DSCA), a quality registration of colorectal surgery in the Netherlands, to make a more accurate comparison of outcome among various hospitals. Future research should reveal optimal skeletal muscle index and quality cutoff points in this specific population. Moreover, it would be of interest to investigate the association between skeletal muscle measurements and oncological outcome and prognosis.

Our study has some limitations. Definitions of sarcopenia and sarcopenic obesity remain under debate. We used definitions based on previous studies [20, 21], which are different than those used in several other studies. A different definition could have led to different results. Moreover, the univariate associations between muscle mass index and outcome, as well as between muscle radiation attenuation and outcome were not calculated for males and females separately, while body composition is not the same between sexes. We used BMI for the definition of sarcopenic obesity based on previous research [7]; however, adipose tissue measurements on the CT scan might be superior to the calculation of BMI. The explorative nature of the skeletal muscle mass analyses at 3 different levels might be both a limitation as well as a strength of our study. For future research, using level L3 might be recommended [33]. But, it remains to be seen whether or not using L3 CT-slices is the best approach. Due to the retrospective and explorative nature of this study, and the limited number of patients, it is subject to potential bias and certain limitations with respect to their internal validity and generalization. Our findings should therefore be interpreted with caution. More research is needed to confirm our results. Since surgery took place between 2007 and 2012, no laparoscopic procedures were performed. Nowadays, to follow a laparoscopic approach is more common and known to result in less complications [34], but the results here may of course only account for non-laparoscopic surgical approaches.

Conclusion

In this explorative manuscript, we found that skeletal muscle radiation attenuation was associated with overall and grade 3–5 (severe) postoperative morbidity after chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications. Skeletal muscle mass and sarcopenia were not associated with postoperative complications. Body composition might be used to identify patients with high risk of worse outcome after surgery, paving the way to select patients that might benefit from preoperative optimization.

Acknowledgments

This study was previously presented at the 10th Sarcopenia, Cachexia and Wasting Disorders (SCWD) conference in Rome, Italy, 8–10 December 2017 and the abstract was published in the Journal of Cachexia Sarcopenia and Muscle 2017 (reference: Abstracts of the 10th International Conference on Cachexia, Sarcopenia and Muscle Wasting, Rome, Italy, 8–10 December 2017 (Part 1). Journal of Cachexia, Sarcopenia and Muscle, 8:1019. doi: 10.1002/jcsm.12255). This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

1 Landelijke werkgroep Gastro Intestinale Tumoren: Landelijke Evidence-Based Richtlijn Colorectaal Carcinoom. www.oncoline.nl/colorectaalcarcinoom, 2014. (accessed October, 2015).

2 Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M: An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 2008;15:2661–2667.

3 Stelzmueller I, Zitt M, Aigner F, Kafka-Ritsch R, Jager R, De Vries A, Lukas P, Eisterer W, Bonatti H, Ofner D: Postoperative morbidity following chemoradiation for locally advanced low rectal cancer. J Gastrointest Surg 2009;13:657–667.

4 van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN: Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg 2012;99:550–557.

5 Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE: Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer 2012;107:931–936.

6 Gendall KA, Raniga S, Kennedy R, Frizelle FA: The impact of obesity on outcome after major colorectal surgery. Dis Colon Rectum 2007;50:2223–2237.

7 Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE: Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629–635.

8 Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, Edil BH, Wolfgang CL, Schulick RD, Choti MA, Kamel I, Pawlik TM: Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB (Oxford) 2011;13:439–446.

9 Hulzebos EH, van Meeteren NL: Making the elderly fit for surgery. Br J Surg 2016;103:463.
10 Heldens AF, Bongers BC, de Vos-Geelen J, van Meeteren NL, Lenssen AF: Feasibility and preliminary effectiveness of a physical exercise training program during neoadjuvant chemoradiotherapy in individual patients with rectal cancer prior to major elective surgery. Eur J Surg Oncol 2016;42:1322–1330.
11 Berkel AE, Woutersen DP, van der Palen J, Klaase JM: Prognostic factors for postoperative morbidity and tumour response after neoadjuvant chemoradiation followed by resection for rectal cancer. J Gastrointest Surg 2014;18:1648–1657.
12 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–196.
13 Dindo D, Demartines N, Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–213.
14 Lee JS, He K, Harbaugh CM, Schaubel DE, Sonnenday CJ, Wang SC, Englesbe MJ, Eliason JL; Michigan Analytic Morphomics Group (MAMG): Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. J Vasc Surg 2011;53:912–917.
15 Hasselager R, Gogenur I: Core muscle size assessed by perioperative abdominal CT scan is related to mortality, postoperative complications, and hospitalization after major abdominal surgery: a systematic review. Langenbecks Arch Surg 2014;399:287–295.
16 Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R: Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985) 1998;85:115–122.
17 Taaffe DR, Henwood TR, Nalls MA, Walker DG, Lang TF, Harris TB: Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults. Gerontology 2009;55:217–223.
18 Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewe KW, Hoofwijk AG, Stoot JH, Von Meyenfeldt MF, Beets GL, Derikx JP, Poeze M: Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg 2015;261: 345–352.
19 Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, Heymsfield SB, Heshka S: Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985) 2004;97:2333–2338.
20 Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, Klaase JM: Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer. Int J Colorectal Dis 2016;31:1117–1124.
21 Jaap K, Hunsinger M, Dove J, McGinty K, Stefanowicz E, Fera J, Wild J, Shabahang M, Blansfield J: Morphometric predictors of morbidity after pancreatectomy. Am Surg 2016;82:1221–1226.
22 Sabel MS, Terjimanian M, Conlon AS, Griffith KA, Morris AM, Mulholland MW, Englesbe MJ, Holcombe S, Wang SC: Analytic morphometric assessment of patients undergoing colectomy for colon cancer. J Surg Oncol 2013;108:169–175.
23 Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, Hiyoshi Y, Iwagami S, Yoshida N, Yoshida M, Watanabe M, Baba H: Sarcopenia is a negative prognostic factor after curative resection of colorectal cancer. Ann Surg Oncol 2015;22:2663–2668.
24 Reisinger KW, Derikx JP, van Vugt JL, Von Meyenfeldt MF, Hulsewe KW, Olde Damink SW, Stoot JH, Poeze M: Sarcopenia is associated with an increased inflammatory response to surgery in colorectal cancer. Clin Nutr 2016;35:924–927.
25 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People: Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412–423.
26 Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, Mazurak VC: Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf) 2014;210:489–497.
27 Visser M, van Venrooij LM, Vulperhorst L, de Vos R, Wisselink W, van Leeuwen PA, de Mol BA: Sarcopenic obesity is associated with adverse clinical outcome after cardiac surgery. Nutr Metab Cardiovasc Dis 2013;23:511–518.
28 O'Doherty AF, West M, Jack S, Grocott MP: Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. Br J Anaesth 2013;110:679–689.
29 Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, Momblan D, Balust J, Blanco I, Martinez-Palli G: Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg 2018;267: 50–56.
30 Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, Poston GJ, Palmer DH, Fenwick SW: Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg 2016;103:504–512.
31 West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S: Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth 2015;114:244–251.
32 Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga ANM, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM: The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial. BMC Gastroenterol 2018; 18:29.
33 Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE: A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33:997–1006.
34 Kolfschoten NE, van Leersum NJ, Gooiker GA, Marang van de Mheen PJ, Eddes EH, Kievit J, Brand R, Tanis PJ, Bemelman WA, Tollenaar RA, Meijerink J, Wouters MW: Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. Ann Surg 2013;257:916–921.